REMARKS

In this Amendment, claims 107, 154, 163, 170, 178, 180, 185, 197, 216 and 217 are currently amended. Claims 110-112, 114, 157-161, 166-169, 173-177, 180-183, 190, 193-196, 199, 199-201, 204-206, and 209-211 were previously presented. Claims 1-106, 108, 109, 113, 115-153, 155, 156, 162, 164, 165, 171, 172, 179, 184, 186-189, 191, 192, 198, 202, 203, 207, 208 and 212-215 are canceled without prejudice or disclaimer. New claims 218-229 are added.

It is submitted that no new matter has been added by virtue of the amended and newly added claims, which are supported by the claims and the disclosure of the application as originally filed. The amendments to claims 107, 216 and 217 relate to form to increase the clarity of each. Claims 154, 163, 170, 178, and 217 are re-written in independent form. Claims 154, 163, 170, 178, and 217 with multiple dependencies are re-written as new dependent claims 221-224 and 218.

Accordingly, the currently pending claims are now claims 107, 110-112, 114, 154, 157-161, 163, 166-170, 173-178, 180-183, 185, 190, 193-197, 199-201, 204-206, 209-211, and 216-229. The currently pending claims are presented to place the application in condition for allowance or in better form for appeal.

Support for the Amended Claims

Support for amended claims 178 and 197 is found in the as-filed specification on page 20, lines 20-31 to page 21, lines 1-6; on page 32, Example 3, lines 1-23; and in Figs. 1D-1F. Support for amended claim 185 is found in the as-filed specification on page 20, lines 20-31 to page 21, lines 1-27.

Support for new claims 219-222 is found in the disclosures of both priority applications (i.e., U.S. Serial Nos. 60/083,917 ("the '917 application"), and 09/302,896, ("the '896 application"), as well as in the instant application. The instant application specifically refers to the muscle-derived cell isolation method of the '896 application, for example, in Example 1 on page 28, lines 29-31 to page 29, lines 1-23 of the instant application; this isolation method is incorporated by reference in the instant application (See, e.g., page 51 of the instant application). The '896 application contains the same pertinent disclosure as does the '917

application at page 81, Example 11. Support for new claims 227-229 is found throughout the specification, including, for example, on page 21, lines 3-5, and 15-23 and on page 20, lines 26 and 29.

Objections to the claims

The Examiner has objected to claim 217, which recites the term "and/or". According to the Examiner, this term is an improper term for listing a group or species. Applicants submit that claim 217 as presently amended moots the Examiner's objection.

The claims fulfill the requirements of 35 U.S.C. §112, first paragraph

Claim 107, 109-112, 114 and 154-217 were rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement. According to the Examiner, the limitation "15 to 40%" is allegedly not supported by the as-filed specification.

Applicants respectfully disagree with the Examiner's assertion. Furthermore, Applicants submit that the presently amended claims 107 and 216, and the claims depending from these claims, comply with the written description requirement and are fully supported by the instant specification. For example, at page 29, lines 14-23 of the specification, Applicants describe the re-plating of non-adherent cells into a second collagen-coated container. Accordingly, withdrawal of this rejection is respectfully requested.

The rejection of claims 109, 155-156, 162, 164-165, 171-172, 179, 184, 186-189, 191-192, 198, 202-203, 207-208 and 212-215 is moot in view of the cancellation of these claims.

Claim 212 and its dependent claims 213-215 were rejected under 35 U.S.C. §112, first paragraph, as allegedly not supporting the recitation "the cutaneous depression, wound, fissure, or opening in an individual". The Examiner's rejection of claim 212 and its dependent claims is moot in view of cancellation of these claims.

Claim 213 was rejected as not having support in the as-filed specification for the recitation "cutaneous depression, wound, fissure, or opening is selected from diverticulae, fistulae or aneurysms". The Examiner's rejection of claim 213 is moot in view of cancellation of claim 213.

Claims 156, 162, 165, 172, 192, 203, 208 and 217 were rejected under 35 U.S.C. §112, first paragraph, for alleged lack of enablement. According to the Examiner, "the specification, while being enabling for using MDCs in a method of augmenting or bulking muscle tissue in a recipient, does not reasonably provide enablement for using cells in a genus of therapeutic methods contemplated by the claimed invention". While Applicants do not agree with this rejection, claims 156, 162, 165, 172, 192, 203 and 208 have been canceled to expedite prosecution of the application to allowance. It is submitted that currently amended claim 217 does not describe the use of cells in a genus of therapeutic methods and overcomes this rejection. Accordingly, withdrawal of the §112, first paragraph rejection is respectfully requested.

The claims fulfill the requirements of 35 U.S.C. §112, second paragraph

Claims 184-189 and 212-215 were rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite. According to the Examiner, the term "an opening in an individual' is a relative term, whose metes and bounds are not defined. It is submitted that amendment and cancellation of the pertinent claims moots this rejection. Withdrawal of the rejection is thus respectfully requested.

The claims satisfy the requirements of 35 U.S.C. §103

Claims 190-194, 196, 197, 199, 201-204 and 206-210 were rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over U.S. Patent No. 5,667,778 to Atala (hereinafter "Atala") taken with U.S. Patent No. 6,261,832 to Law (hereinafter "Law").

It is submitted that the rejection of claims 191-192, 202-203, and 207-208 is moot in view of the cancellation of these claims.

The Examiner admits at page 12, lines 3-4, of the Office Action that Atala does not teach using skeletal muscle cells in the method of treating conditions involving gastrointestinal tract and urinary tract. The Examiner also states that Law teaches a method of augmenting muscle tissue using myogenic cells, which can be of skeletal, smooth or cardiac origin. The

Examiner further opines that it would have been obvious to use skeletal myogenic cells of Law in Atala's method of augmenting or bulking bladder or sphincter tissue.

The rejection of the claims under 35 USC § 103(a) is respectfully traversed. Applicants respectfully contend that the Examiner has not established a *prima facie* case of obviousness under 35 U.S.C. § 103 as a basis for rejection of these claims.

It is respectfully submitted that the presently claimed invention must be considered as a whole in determining differences between the prior art and the presently claimed invention. M.P.E.P. §2141.02. Considered in its entirety, the presently claimed invention is directed to methods involving the injection of isolated **skeletal** muscle derived progenitor muscle cells into sites of specified **smooth** muscle tissue, namely, esophagus, bladder, sphincter, or ureteral-bladder, as well as skin tissue, to augment or bulk these types of tissues after injection. In addition, the skeletal muscle-derived progenitor muscle cells may be isolated by a particular enrichment protocol prior to use. Applicants' skeletal muscle derived cells augment or bulk the smooth muscle tissue or skin tissue into which they are injected as they survive over long time periods and enhance the smooth muscle tissues or skin tissue, essentially without adverse problems such as inflammation.

Applicants respectfully contend that the Examiner has not provided evidence, either in the cited references or in the prior art as a whole, of a valid suggestion or motivation to combine and/or modify the disclosures of Atala and Law to produce the methods of the present invention. There is also no evidence provided by the Examiner to suggest that the combined disclosures of Atala and Law would lead to the achievement of the presently claimed invention. The Examiner provides only conclusive statements, without further support or evidence, that "Law teaches that either skeletal or smooth cells can be used in a method of augmenting muscle tissue" and that "one of ordinary skill in the art would have been motivated to use skeletal muscle cells instead of smooth muscle cells in the method taught by Atala." Without further support or evidence, these statements do not serve as a valid basis to suggest to, or to motivate, a skilled practitioner in the art to combine Atala, which teaches using **smooth** muscle cells to treat **smooth** muscle defects, with Law, which teaches using **skeletal** muscle cells to treat skeletal muscle defects. Atala does not remotely mention that **skeletal**

muscle cells described by Law would be suitable or desirable to treat vesicoureteral reflux, incontinence and other bladder **smooth** muscle defects. As noted in MPEP §2143.01, with reference to *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990):

> The mere fact that references can be combined or modified does not render the resultant combination obvious unless **the prior art suggests** the desirability of the combination. [Emphasis added]

Furthermore, Applicants respectfully submit that practitioners in the art appreciate that skeletal muscle and smooth muscle cells and tissue are dissimilar in numerous ways, as shown by the enclosed Table 8-3, in Chapter 8 (Muscle Physiology), *In*: *Human Physiology, From Cells to Systems,* (1989), Ed. Lauralee Sherwood, West Publishing Co. St. Paul, MN, pages 250-251. While Atala teaches the use of bladder **smooth** muscle cells to treat bladder **smooth** muscle defects in the presence of a polymeric substance and Law teaches **skeletal** myoblast cells to treat **skeletal** muscle neurodegenerative defects, Applicants' presently claimed invention is drawn to methods in which isolated **skeletal** muscle-derived progenitor cells augment or bulk particular **smooth** muscle tissues or skin tissue. In view of these disparate teachings of the cited art, and considering the knowledge of the physiological differences between smooth and skeletal muscle cells and tissues, there is no suggestion or teaching provided by Atala, Law, or the art that would lead one of skill in the art to combine the teachings of these references so as to arrive at Applicants' presently claimed invention.

In fact, if one were to combine Atala and Law, one would not be led to make the modifications necessary to achieve Applicants' invention as claimed, based on the teachings of these references considered for all that they offer, and in view of knowledge in the art. Without a suggestion or motivation in the references or in the art to combine these two references, the § 103 rejection is inappropriate and should be withdrawn.

Further, it is submitted that all claim limitations must be taught or suggested by the cited art reference. M.P.E.P. §2143.03. However, the applied references, alone or in combination, do not teach or suggest each and every element of Applicants' claimed invention. For example, neither Atala nor Law, alone or in proper combination, teach Applicants' presently claimed methods which involve the injection of **skeletal** muscle derived progenitor

cells into **smooth** muscle of the esophagus, bladder, sphincter, ureteral-bladder, or skin tissue to augment or bulk these types of smooth muscle and skin tissue after injection. Rather, Atala specifically describes the use of bladder smooth muscle cells in his contemplated methods of treating smooth muscle defects by mixing the bladder muscle cells with a liquid polymatrix material; and Law specifically teaches myoblasts, taken from skeletal muscle biopsies, which are injected into skeletal muscle sites, such as the whole body, to treat neuromuscular degenerative disease and genetic neurodegenerative diseases.

In addition, Law only describes his contemplated invention as providing "compositions and methods for repairing degenerating cells and replenishing lost cells in patients with hereditary or degenerative diseases, in particular those characterized by muscle malfunction, degeneration and weakness." (Col. 7, lines 16-29 of Law). It is in the context of his contemplated invention of treating muscle diseases, such as muscular dystrophy, that Law states that "any myogenic cell can be used." (See, Col 7, lines 16-36 of Law). Thus, Law does not teach or disclose Applicants' claimed invention.

Further, Law is silent regarding the augmentation or bulking of specified smooth muscle tissue types. Law does not teach injecting skeletal muscle-derived progenitor cells into smooth muscle tissue sites such that the injected cells augment and bulk the smooth muscle tissues, particularly those that are specified by Applicants' presently claimed invention. Accordingly, Atala and Law in combination do not teach or suggest that isolated **skeletal** derived early muscle cells will survive over time in areas of physiologically different muscle tissue to provide augmented or bulked **smooth** muscle and skin tissue in a recipient.

It is also submitted that the combined teachings of Atala and Law, and further in view of the knowledge in the art, do not provide a reasonable expectation of success that skeletal muscle-derived progenitor cells could augment or bulk non-skeletal, i.e., specified smooth muscle tissues and skin tissue, after being injected into areas of the smooth muscle or skin tissues as is required by Applicants' presently claimed invention. On the one hand, Atala uses bladder derived muscle cells and injects them into bladder sites. On the other hand, in its disclosure related to whole body injection studies of patients having skeletal muscle disease, Law teaches (1) the use of fresh skeletal muscle biopsies to culture myoblasts from satellite

cells in the biopsies (Col. 12, lines 55-65 or Col. 6, lines 43-57 of Law), and (2) the use of skeletal myoblasts injected into the gastrocnemius muscles of mice to evaluate various types of injection strategies in the skeletal muscle sites (Col. 13, lines 50-67 to Col. 14, lines 1-24 of Law).

The combination of Atala and Law neither suggests nor contemplates Applicants' presently claimed methods involving the injection of skeletal muscle derived MDCs into areas of the esophagus, bladder, sphincter, ureteral-bladder, or skin tissue to augment or bulk these types of smooth muscle and skin tissue after injection. Thus, there no motivation provided by the teachings of Atala and Law, taken in combination, that would lead one having ordinary skill in the art to make the modifications necessary to arrive at Applicants' presently claimed invention.

In view of the foregoing, Applicants respectfully submit that it would not have been *prima facie* obvious to a person of ordinary skill in that art at the time of Applicants' invention to combine the teaching of Atala and Law, namely to use skeletal myogenic cells in the method of augmenting or bulking bladder or sphincter muscle tissue, as opined by the Examiner. (12/20/2004 Office Action, page 12). One having skill in the art, confronted with the different nature of skeletal versus smooth muscle cells and tissue, and based on the teachings and exemplification of Atala and Law, each considered in their entireties and in combination, would be expected to use smooth muscle cells to treat smooth muscle defeats or problems according to Atala and skeletal muscle cells to treat skeletal muscle defects or problems according to Law.

Also, it would not be reasonably expected that one could use **skeletal** muscle derived muscle progenitor cells to augment or bulk the **smooth** muscle tissues or skin tissue, as specified by Applicants, based on the combined teachings of the cited references. The cited references, in combination, do not provide a reasonable expectation that injected skeletal muscle derived cells would survive over time and be able to augment or bulk a different type of muscle tissue, such as smooth muscle tissue. Accordingly, Applicants respectfully request that the §103(a) rejection of claims 190-194, 196, 197, 199, 201-204 and 206-210 over Atala in view of Law be withdrawn.

Claims 190-197 and 199-211 were rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Atala taken with Law, as applied to claims 190-194, 196, 197, 201-204, 206-210 above, and further in view of U.S. Patent No. 5,206,028 to Li (hereinafter "Li").

It is respectfully submitted that the rejection of claims 191-192, 202-203 and 207-208 is moot in view of cancellation of these claims.

According to the Examiner, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teachings of Atala and Law in further view of Li to use a collagen sponge material in the method of augmenting or bulking muscle tissue.

As discussed at length above, the combination of the teachings of Atala and Law, considered in their entireties, does not make obvious Applicants' invention, which provides methods of augmenting or bulking smooth specified muscle tissue or skin tissue using isolated skeletal muscle-derived cells injected into areas of the smooth muscle or skin tissue.

It is respectfully submitted that the combined teachings of the cited references and knowledge in the art would lead one having skill in the art away from the presently claimed invention. Based on the teachings of Atala and Law, one skilled in the art is instead led to treat a smooth muscle defect or disorder with a smooth muscle cell type and to treat a skeletal muscle defect or disorder with a skeletal muscle cell type. The combination of these references does not teach or suggest the use of isolated skeletal muscle derived progenitor cells to augment or bulk the particular types of smooth muscle tissues and skin tissue in methods described by Applicants. It is Applicants' own disclosure that provides to the art methods involving the use of isolated skeletal muscle-derived progenitor cells to augment or bulk specified types of smooth muscle tissue or skin tissue and the survivability of the cells in such smooth muscle or skin tissue.

Turning to Li, Applicants submit that Li teaches a dense collagen membrane matrix material and method of making such material. Li fails to teach and does not contemplate that the described collagen matrix material is used in methods of augmenting or bulking specified types of smooth muscle tissue or skin tissue by injecting into the smooth muscle tissue or skin

tissue isolated skeletal muscle-derived progenitor cells, which survive, and augment or bulk the smooth muscle or skin tissue as provided by Applicants' presently claimed invention. Li's teaching does not compensate for the above-described deficiencies of the primary and secondary references. Combining Atala and Law in consideration of the teaching of Li would not lead one having skill in the art to arrive at Applicants' presently claimed invention for the reasons detailed above.

It is therefore respectfully submitted that the combination of Atala and Law in view of Li does not negate the patentability of Applicants' presently claimed invention. Withdrawal of this rejection is thus respectfully requested.

Double Patenting

Claims 170-173, 175, 176 and 206-211 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 260-272 and 274-279 of copending patent application U.S. Serial No. 09/302,896 ("the '896 application"). According to the Examiner, the conflicting claims are not identical, but are considered to be not patentably distinct from each other because the instant claims and the claims of the '896 application are drawn to a method of ameliorating weakness in the bladder muscle tissue using muscle derived cells.

Applicants respectfully disagree that claims 260-272 and 274-279 of the '896 application are drawn to a method of ameliorating weakness in the bladder muscle tissue using muscle derived cells. The cited claims in the '896 application are directed to a method of ameliorating stress urinary incontinence (SUI) involving injecting myoblasts into a site of injured, damaged, or dysfunctional urethra, sphincter, or a combination thereof, to ameliorate the SUI. These claims are patentably distinct from Applicants' presently amended claims which are drawn to methods in which isolated skeletal muscle derived progenitor cells are injected into esophageal, bladder, sphincter, ureteral-bladder, smooth muscle tissues, or skin tissue to augment or bulk the specified smooth muscle tissue or skin tissue. Accordingly, Applicants request reconsideration and withdrawal of the double patenting rejection.

CONCLUSION

Applicants respectfully submit that the application is now in condition for allowance. An action progressing this application to issue is courteously urged.

Should any additional fees be deemed to be properly assessable in this application for the timely consideration of this amendment and response, or during the pendancy of this application, the Commissioner is hereby authorized to charge any such additional fee(s), or to credit any overpayment, to Deposit Account No. **50-0311**, Reference no. **28682-510-CIP,** Customer Number: **35437**.

Should an extension of time be required for the timely consideration of this Amendment and response, the Commissioner is hereby authorized to grant any such extension of time as may be necessary, and to charge any additional fee(s) owed by Applicants for such extension of time, to the above-mentioned Deposit Account, Reference and Customer Numbers.

If the Examiner believes that it would be helpful to discuss the application to advance the prosecution of the application and claims to allowance, he is respectfully requested to telephone applicants' undersigned representative at (212) 692-6742 and is assured of full cooperation in this effort.

Respectfully submitted,

MINTZ, LEVIN, COHN, FERRIS, GLOVSKY AND POPEO, P.C.

Date: March 17, 2005

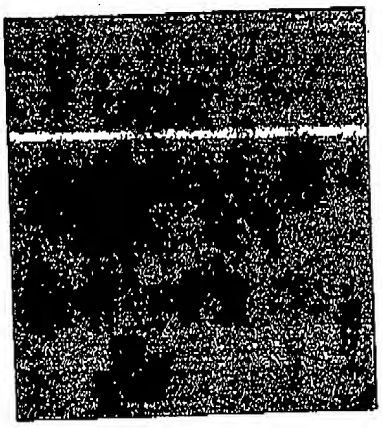
By: Leslie A. Serunian
Leslie A. Serunian
Registration No. 35,353

Correspondence Address:
MINTZ, LEVIN, COHN, FERRIS,
GLOVSKY AND POPEO, P.C.
Chrysler Center
666 Third Avenue
New York, New York 10017
Telephone: (212) 935-3000
Facsimile: (212) 983-3115
Direct Tel.: (212) 692-6742

Express Mail Label No.: EV 627295296US

HUMAN PHYSIOLOGY

FROM CELLS TO SYSTEMS



Lauralee Sherwood

DEPARTMENT OF PHYSIOLOGY
SCHOOL OF MEDICINE
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WEST PUBLISHING COMPANY

St. Paul ■ New York ■ Los Angeles ■ San Francisco

Text copyediting Judith Lary, Naples Editing Service
Art copyediting Jo-Anne Naples, Naples Editing Service
Composition Rolin Graphics
Artwork Wayne Clark, Cyndie Clark-Huegel, Darwen and Vally Hennings, Sandra McMahon, Rolin Graphics, and John and Judy Waller. Individual credits follow Index.
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Cover design David J. Farr/IMAGESMYTHE Inc.
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Printed in the United States of America

96 95 94 93 92 91 90 89 8 7 6 5 4 3 2 1 0

Library of Congress Cataloging-in-Publication Data

Sherwood, Lauralee.
Human physiology.

Includes bibliographies and index.
1. Human physiology. I. Title. [DNLM: 1. Anatomy. 2. Physiology. QT 104 S554h]
QP34.5.S48 1989 612 88-37830
ISBN 0-314-47230-4

CHAPTER 8

MUSCLE PHYSIOLOGY

CHAPTER CONTENTS AT A GLANCE

INTRODUCTION *The Olympic athlete stands triumphantly on the winner's stand, tears of pride and joy flowing freely as the precious gold medal is slipped on. Muscles have performed skillfully and powerfully at the athlete's command. The years of training, willfully pushing the muscles to ever greater feats, have paid off. Skeletal muscles are the only organs in the body over which we have conscious, voluntary control. How does muscle excitation bring about contraction? How can contractions of varying strength in the same muscle be accomplished? How can training alter muscle performance? These are some of the questions that will be answered as you read on.*

Table 8–3 Comparison of Muscle Types

Characteristic	Type of Muscle. *Skeletal*	*Multiunit Smooth*	*Single-Unit Smooth*	*Cardiac*
Location	Attached to skeleton	Large blood vessels, eye, and hair follicles	Walls of hollow organs in digestive, reproductive, and urinary tracts and in small blood vessels	Heart only
Function	Movement of body in relation to external environment	Varies with structure involved	Movement of contents within hollow organs	Pumps blood out of heart
Mechanism of contraction	Sliding-filament mechanism	Uncertain; may involve shortening of contractile unit in corkscrew fashion	Uncertain; may involve shortening of contractile unit in corkscrew fashion	Sliding-filament mechanism
Innervation	Somatic nervous system (alpha motor neurons)	Autonomic nervous system	Autonomic nervous system	Autonomic nervous system
Level of control	Under voluntary control; also subject to subconscious regulation	Under involuntary control	Under involuntary control	Under involuntary control
Initiation of contraction	Neurogenic	Neurogenic	Myogenic (pacemaker activity and slow-wave potentials)	Myogenic (pacemaker activity)
Role of nervous stimulation	Initiates contraction; accomplishes gradation	Initiates contraction; contributes to gradation	Modifies contraction; can excite or inhibit; contributes to gradation	Modifies contraction; can excite or inhibit; contributes to gradation
Modifying effect of hormones	No	Yes	Yes	Yes
Presence of thick myosin and thin actin filaments	Yes	Yes	Yes	Yes
Striated due to orderly arrangement of filaments	Yes	No	No	Yes
Presence of troponin and tropomyosin	Yes	No	No	Yes
Presence of T tubules	Yes	No	No	Yes (large)

and tropomyosin from their blocking position so that actin and myosin are free to bind with each other. Smooth-muscle Ca^{++} binds with *calmodulin*, an intracellular protein found in most cells that is structurally similar to troponin (see p. 64). This Ca^{++}-calmodulin complex binds to and activates another protein, **myosin kinase**, which in turn phosphorylates myosin. Phosphorylated myosin then binds with actin so that cross-bridge cycling can begin. When Ca^{++} is removed, myosin is dephosphorylated and can no longer interact with actin, so the muscle relaxes. Thus, smooth muscle is triggered to contract by a rise in cytosolic Ca^{++} similar to in skeletal muscle. In smooth muscle, however, Ca^{++} ultimately turns on the cross bridges by inducing a chemical change in myosin in the thick filaments, whereas in skeletal muscle it exerts its effect by invoking a physical change at the thin filaments.

The means by which excitation brings about an increase in

Table 8-3 Comparison of Muscle Types (continued)

Characteristic	Type of Muscle			
	Skeletal	*Multiunit Smooth*	*Single-Unit Smooth*	*Cardiac*
Level of development of sarcoplasmic reticulum	Well developed	Poorly developed	Poorly developed	Moderately developed
Cross bridges turned on by Ca^{++}	Yes	Yes	Yes	Yes
Source of increased cytosolic Ca^{++}	Sarcoplasmic reticulum	Extracellular fluid and sarcoplasmic reticulum	Extracellular fluid and sarcoplasmic reticulum	Extracellular fluid and sarcoplasmic reticulum
Site of Ca^{++} regulation	Troponin in thin filaments	Myosin in thick filaments	Myosin in thick filaments	Troponin in thin filaments
Mechanism of Ca^{++} action	Physically repositions troponin-tropomyosin complex to uncover actin cross-bridge binding sites	Chemically brings about phosphorylation of myosin cross bridges so they can bind with actin	Chemically brings about phosphorylation of myosin cross bridges so they can bind with actin	Physically repositions troponin-tropomyosin complex
Presence of gap junctions	No	Yes (very few)	Yes	Yes
ATP used directly by contractile apparatus	Yes	Yes	Yes	Yes
Myosin ATPase activity; speed of contraction	Fast or slow, depending on type of fiber	Very slow	Very slow	Slow
Means by which gradation accomplished	Varying number of motor units contracting (motor-unit recruitment) and frequency at which they're stimulated (wave summation)	Varying number of muscle fibers contracting and varying cytosolic Ca^{++} concentration in each fiber by autonomic and hormonal influences	Varying cytosolic Ca^{++} concentration by myogenic activity and via influences by autonomic nervous system, hormones, mechanical stretch, and local metabolites	Varying length of fiber (depending on extent of filling) and varying cytosolic Ca^{++} concentration through autonomic, hormonal, and local metabolite influence
Presence of tone in absence of external stimulation	No	No	Yes	No
Clear-cut length-tension relationship	Yes	No	No	Yes

cytosolic Ca^{++} concentration in smooth-muscle cells also differs from that for skeletal muscle. A smooth-muscle cell has no T tubules and a poorly developed sarcoplasmic reticulum. The increased cytosolic Ca^{++} that triggers the contractile response comes from two sources: some Ca^{++} is released intracellularly from the meager sarcoplasmic reticulum stores, but most enters down its concentration gradient from the ECF as Ca^{++} channels in the plasma membrane are opened. Because smooth-muscle cells are so much smaller in diameter than skeletal-muscle fibers, this Ca^{++} influx from the ECF is able to influence cross-bridge activity, even in the central portions of the cell, without the necessity of an elaborate T tubule-sarcoplasmic reticulum mechanism. Relaxation is accomplished by removal of Ca^{++} as it is actively transported back into the sarcoplasmic reticulum and out across the plasma membrane.